

QUALIFIED HEALTH CLAIM PETITION
100% WHEY PROTEIN PARTIALLY HYDROLYZED
in Infant Formula and
REDUCING THE RISK OF ALLERGY IN INFANTS

EXECUTIVE SUMMARY

The prevalence of allergic (atopic) diseases continues to rise in developing countries, and even more markedly in developed countries. Worldwide, all allergic manifestations: dermatologic, respiratory, and gastrointestinal, are significantly increasing. Although genetic predisposition plays a role in development of allergy on an individual basis, these global increases are more likely associated with changes in environmental factors and antigenic exposure. In infancy, atopic dermatitis is the most common chronic skin disorder, and its prevalence continues to rise. In some developed populations up to 20% of infants can be affected. Atopic disease, and atopic dermatitis specifically, are not only an increasing cause of morbidity, they also place major burdens on quality of life for patients and their families and increase direct and indirect associated healthcare costs. In addition, recent evidence suggests that atopic dermatitis in infancy may be an important “point of entry” for the development of atopic manifestations later in life, a process described in the scientific literature as the “atopic march”. These developments place significant importance and urgency on the need to develop and provide strategies for the prevention atopic disease in infants.

Multiple prevention strategies are being sought by the pediatric community. Ultimately the most beneficial strategies will be those that are efficacious, cost effective, and acceptable to the broadest possible segment of the population. Because food antigens are recognized as being among the most common antigens that can trigger atopic disease in

infancy, significant scientific investigation has focused on modifications to antigenic exposure early in life. Cow's milk proteins are major antigens to which many infants are exposed early in life, particularly infants who are not exclusively breastfed and who receive infant formulas based on standard intact cow's milk protein. Consequently, the modification of these proteins, typically by enzymatic hydrolysis to reduce their allergenicity, has been increasingly studied over the last two decades as a logical alternative for prevention of atopic disease.

To date, various formulas containing hydrolyzed proteins, including both casein-based extensively hydrolyzed formulas and whey-based partially hydrolyzed formulas, have been studied for their potential efficacy in the primary prevention of atopic disease. Extensively hydrolyzed formulas (EHF) are currently recommended by the American Academy of Pediatrics both for therapeutic use, once infants develop atopic disease, *and* for the primary prevention of allergy.

As a result of improved technology, 100% Whey-Protein Partially Hydrolyzed formulas (PHF-W) became available in the late 1980's. This type of formula has taste comparable to standard intact protein formulas, which generally leads to better acceptance than other hydrolysates by infants and their caregivers – an important factor in the potential for implementation of any primary prevention strategy. In addition, PHF-W are commercialized in the US as routine infant formulas, at prices comparable to other routine formulas.

A number of studies have been undertaken to assess the potential role of PHF-W in the prevention of allergy in infants. These studies (including 18 publications of prospective, controlled clinical trials in 12 distinct cohorts of healthy infants fed Nestlé PHF-W) have all

shown varying degrees of reduction in the incidence of allergy, and particularly atopic dermatitis, with PHF-W as compared to standard intact cow's milk protein formulas (CMF). The size, scientific quality, and degree of statistical significance in these trials have varied. However, each of these trials has documented a *decrease* in incidence of allergy when comparing PHF-W to CMF. The degree of reduction in the risk of developing any atopic disease has also varied in these trials, with risk reduction ranging between 32 and 88%. In no trial to date has an *increase* in allergic risk been documented for PHF-W when compared to CMF. The resulting substantial body of literature strongly supports the role of PHF-W in the primary prevention of allergy in infants.

An important part of this cumulative body of evidence is a recently published, independent, large, well-conducted multicenter trial. In March 2003, von Berg and colleagues published their 1-year follow-up of the German Infant Nutritional Intervention (GINI) study. This is a comparison of CMF, PHF-W, extensively hydrolyzed whey formula (EHF-W), and extensively hydrolyzed casein formula (EHF-C) in infants at risk for atopic disease. The group given EHF-C had significantly less atopic disease, overall, at one year of follow-up than the group fed CMF. When atopic dermatitis (the most common allergic symptom in this study as well as in infants in general) was considered alone, both the group fed EHF-C and the group fed PHF-W had significantly reduced incidence compared to the CMF group.

Further demonstration of the benefit of PHF-W in primary prevention has been documented with longer follow-up data, as seen in studies of seven cohorts that followed subjects up to as many as five years of age and showed a reduced incidence of allergic manifestations, as compared to CMF-fed infants. Although not yet published, the 3-year

GINI follow-up data presented at the European Academy of Allergology and Clinical Immunology meeting (EAACI; Paris 2003) and other national and international meetings, are consistent with the results of the previously published long-term follow-up studies in other subject cohorts in demonstrating a reduction in the risk of atopic disease.

EHF-C formulas have also been studied for primary prevention, and in each case (again with varying degrees of study size, quality, and statistical significance) EHF-C have shown efficacy in reducing the risk of development of atopic disease compared to CMF. Although there have been many more studies on PHF-W than on EHF-C with regard to preventive impact, the fact that both types of hydrolysate formulas have a role in reducing the risk of allergy is apparent. Only the GINI study has compared the performance of both types of hydrolysates concurrently with CMF. Notably, no statistically significant difference in performance relative to allergy prevention between PHF-W and EHF-C was reported in GINI.

Finally, a recent independent meta-analysis carried out by the Cochrane Library assessed all the available literature on the use of hydrolyzed protein formulas for prevention of allergy. The Cochrane Library published the conclusions of authors Osborn *et al.* in 2003: “In high risk infants [infants with a positive family history of allergy], who are unable to be completely breast-fed, there is evidence that prolonged feeding with a hydrolysed, compared to cow’s milk formula reduces infant and childhood allergy and infant [cow’s milk allergy].” The Osborn meta-analysis goes on to conclude that “Further trials are required to determine if significant clinical benefits persist beyond five years of age and if there is any additional benefit from use of an extensively compared to a partially hydrolysed formula. Incremental costs of formula and the effect on compliance should be measured.”

In assessing the allergy-prevention effect of a hydrolysate formula, it appears that neither the degree of hydrolysis nor the protein source, alone, is sufficient to predict efficacy. Based on the GINI study, where an extensively hydrolyzed whey formula (not previously studied) failed to show a preventive effect, it can be speculated that the methodology used for the hydrolysis of the proteins used may also be critical in determining performance. In addition, very few studies are available on partially hydrolyzed *combinations* of whey and casein, and only one of these studies (which was limited to a six-month follow-up) has demonstrated a statistically significant reduction in allergic disease. Thus, before assuming that a particular protein hydrolysate formula is effective in reducing the risk of allergy, a careful evaluation of the attributes of both the protein hydrolysate and the formula matrix must be conducted. Clinical trials may be necessary to confirm the beneficial effect.

It is important to note that the vast majority of studies have been carried out in populations of infants with a family history of allergy. For both practical as well as ethical reasons, these studies have been in populations of infants for whom a higher risk of developing allergy can be identified. It is well documented that infants with a family history of allergy have a higher risk of developing atopic disease. Yet, while these infants may be referred to as “high risk” or “at risk” by researchers, it is important to note that only healthy infants with no manifestations of allergic disease are accepted into these primary prevention studies.

Currently, family history is the only factor that can be used in general clinical practice to assess the risk of infants for development of allergy. Unfortunately, family history is a poor method for assessing the risk for an individual infant or for identifying most

of the infants at risk in the general population. In fact, approximately 50% of infants who go on to develop atopic disease (and, therefore, were indeed at risk) do not have a family history of allergy. In addition, for all those infants who *could* be identified as being at risk by a thorough family history, there is currently no standardized, accepted or practical mechanism to obtain this history prior to exposing these infants to intact cow's milk protein. As a result, the vast majority of infants at risk of developing atopic disease go unidentified. Therefore, interventions appropriate for the general population of infants are both desirable and necessary.

Given the availability of data from such a recent, large trial as the GINI study, and in light of the large volume of consistent data accumulated over the last 20 years and independent meta-analyses documenting efficacy, a strong case can be made for the role of PHF-W in reducing the risk of allergy in infants who receive infant formula. Two PowerPoint presentations giving an overview of this case and an introduction to this petition as presented to FDA on April 29, 2005, are enclosed at Appendix A-I. The case may also be restated, specifically and in short, as follows:

1. The majority of infants at risk of developing allergies (atopic disease) are not accurately predicted based on current, usual clinical practice tools, including reliance on family history;
2. Consequently, a significant number of infants in the general population may be placed at risk of developing food allergy when fed standard intact cow's milk protein based formulas;
3. The palatability, long history of safe use of PHF-W in the general population, and cost comparable to standard intact cow's milk formulas make it acceptable to young infants and their caregivers as a routine infant formula – as demonstrated by the fact that it is currently fed to nearly 50% of the infants in several states as the formula of first choice in their state WIC programs; and

4. The current body of clinical and scientific evidence supports the use of 100% Whey-Protein Partially Hydrolyzed formulas, in preference to standard intact cow's milk protein formulas as routine substitute or supplement to human milk, for the primary prevention of atopic disease in those infants who do not get all the benefits of exclusive breastfeeding.

Given the fact that the majority of children actually at risk for atopic disease cannot be adequately identified, and given both the potential protective effect and the affordability of PHF-W – the use of 100% Whey-Protein Partially Hydrolyzed formulas constitutes a practical and cost effective strategy for primary prevention of atopic disease for infants in the general population who require supplements or alternatives to breast milk, and who are not known to be allergic to cow's milk. Nestlé believes that providing information relative to general infant feeding practices that may carry such a benefit fulfills not only a need, but also a responsibility to consumers and the general public.

In order to make this important information available to parents and caregivers who choose to use formula, but may wish to help reduce the risk of allergy in their infants, the following model qualified health claim language is proposed:

Breastfeeding is the best way to nourish infants. For infants who are not exclusively breastfed, emerging clinical research in healthy infants with family history of allergy shows that feeding a 100% Whey-Protein Partially Hydrolyzed formula may reduce the risk of common food allergy symptoms, particularly allergic skin rash, when used instead of whole-protein cow's-milk formula from the initiation of formula feeding.

Partially hydrolyzed formulas are not intended to treat existing food allergy symptoms. If you suspect your baby is already allergic to milk, or if your baby is on a special formula for the treatment of allergy, your baby's care should be under a doctor's supervision.